

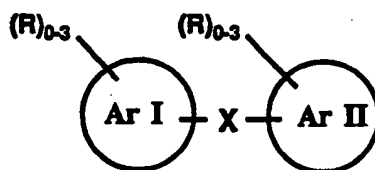


INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁵ : C07C 43/21, C07D 215/18 C07D 215/20, 43/21 A61K 31/44, 31/50, 31/495	A1	(11) International Publication Number: WO 92/20642 (43) International Publication Date: 26 November 1992 (26.11.92)
(21) International Application Number: PCT/US92/03736 (22) International Filing Date: 6 May 1992 (06.05.92) (30) Priority data: 698,420 10 May 1991 (10.05.91) US (60) Parent Application or Grant (63) Related by Continuation US 698,420 (CIP) Filed on 10 May 1991 (10.05.91) (71) Applicant (for all designated States except US): RHONE-POULENC RORER INTERNATIONAL (HOLDINGS) INC. [US/US]; 40 Cape Henlopen Drive, Lewes, DE 19958 (US). (72) Inventors; and (75) Inventors/Applicants (for US only) : SPADA, Alfred, P. [US/US]; 473 Painter Way, Lansdale, PA 19446 (US). MAGUIRE, Martin, P. [US/US]; 649 S. Henderson Road, A-512, King of Prussia, PA 19406 (US). PERSONS, Paul, E. [US/US]; 649 S. Henderson Road, A-507, King of Prussia, PA 19406 (US). MYERS, Michael, R. [US/US]; 205 Lincoln Road, Reading, PA 19606 (US).	(74) Agents: NICHOLSON, James, A. et al.; Rhone-Poulenc Rorer Inc., 500 Arcola Road, P.O. Box 1200, Collegeville, PA 19426 (US). (81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC (European patent), MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, RU, SD, SE, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent), US. Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: BIS MONO-AND BICYCLIC ARYL AND HETEROARYL COMPOUNDS WHICH INHIBIT EGF AND/OR PDGF RECEPTOR TYROSINE KINASE.		
(57) Abstract This invention relates to bis mono- and/or bicyclic aryl and/or heteroaryl compounds exhibiting protein tyrosine kinase inhibition activity. More specifically, it relates to the method of inhibiting abnormal cell proliferation in a patient suffering from a disorder characterized by such proliferation comprising the administration thereto of an EGF and/or PDGF receptor inhibiting effective amount of said bis mono- and/or bicyclic aryl and/or heteroaryl compound and to the preparation of said compounds and their use in pharmaceutical compositions used in this method.		

WE CLAIM:

- 5 1. A method of inhibiting abnormal cell proliferation in a patient suffering from a disorder characterized by such proliferation comprising the administration thereto of an EGF and/or PDGF receptor inhibiting effective amount of a compound having a bis ring system wherein the first ring is aryl or heteroaryl and the second ring is aryl, heteroaryl, carbocyclic or
- 10 heterocarbocyclic and wherein said rings comprise either a substituted or unsubstituted monocyclic ring containing 0 to about 2 hetero atoms, or a bicyclic ring containing 0 to about 4 hetero atoms, or a pharmaceutically acceptable salt thereof.
- 15 2. A pharmaceutical composition for inhibiting abnormal cell proliferation comprising, in admixture with a pharmaceutically acceptable carrier, a pharmaceutically effective amount of a compound according to claim 1.
- 20 3. A method according to claim 1 comprising administering to said patient a pharmaceutically effective amount of a pharmaceutical composition containing, in admixture with a pharmaceutically acceptable carrier, a compound, or a pharmaceutically acceptable salt thereof, of the formula:



25

wherein

Ar I is a substituted or unsubstituted mono- or bicyclic aryl or heteroaryl ring system of about 5 to about 12 atoms and where each monocyclic ring may contain 0 to about 3 hetero atoms, and each bicyclic ring may contain 0 to

30 about 4 hetero atoms selected from N, O and S provided said hetero atoms are not vicinal oxygen and/or sulfur atoms and where the substituents may be located at any appropriate position of the ring system and are described by R.;

Ar II may be as described for Ar I or it may also be saturated carbocyclic wherein said ring comprises either a substituted or unsubstituted

monocyclic ring containing 0 to about 2 hetero atoms, or a bicyclic ring containing 0 to about 4 hetero atoms;

X is $(\text{CHR}_1)_{0-4}$ or $(\text{CHR}_1)_m\text{-Z-(CHR}_1)_n$;

5

Z is O, NR' , S, SO or SO_2 ;

m and n are 0-3 and $m+n=0-3$;

10

R substitution besides hydrogen independently includes alkyl, alkenyl, phenyl, aralkyl, aralkenyl, hydroxy, alkoxy, aralkoxy, acyloxy, halo, haloalkyl, amino, mono- and di-alkylamino, acylamino, carboxy, carbalkoxy, carbaralkoxy, carbalkoxyalkyl, carbalkoxyalkenyl, amido, mono- and dialkylamido and N,N-cycloalkylamido;

15

R and R together may also be keto;

R_1 and R' are hydrogen or alkyl; or

20

a pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition for inhibiting cell proliferation comprising, in admixture with a pharmaceutically acceptable carrier, a pharmaceutically effective amount of a compound according to claim 3.

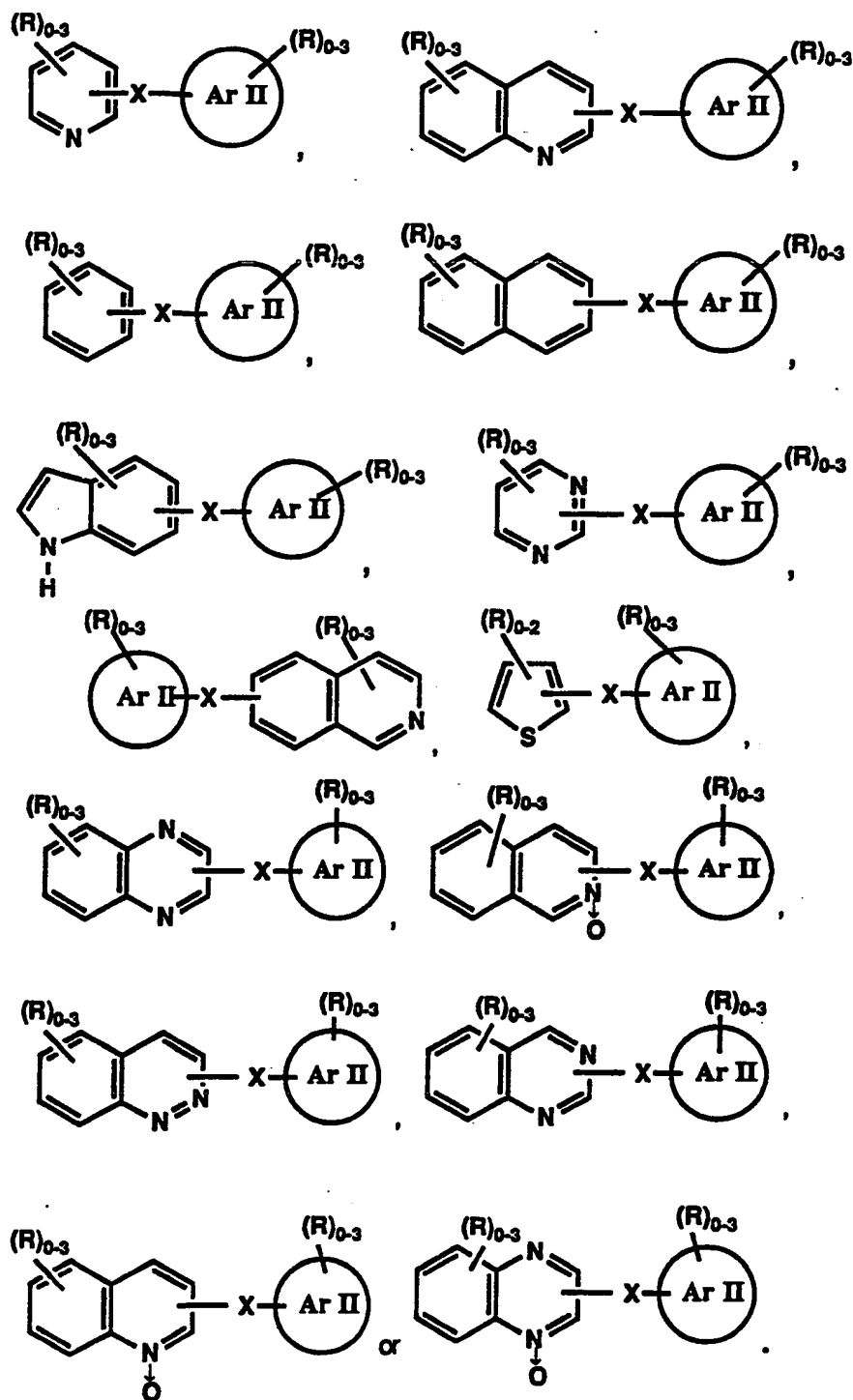
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5. A method according to claim 3 where Ar I and Ar II are independently selected from phenyl, naphthyl, 2-(1H)pyridonyl, pyridyl, quinoliny, thienyl, 1(2H)-isoquinolonyl, indolyl, naphthyridenyl, benzothiazolyl, quinoxaliny, benzomidazolyl, quinoliny-N-oxide, isoquinoliny-N-oxide, quinazolinyl, quinoxaliny-N-oxide, quinazolinyl-N-oxide, benzoxazinyl, phthalazinyl, or cinnoliny; and R is selected from hydrogen, alkyl, alkoxy, hydroxy, halo or trifluoromethyl.

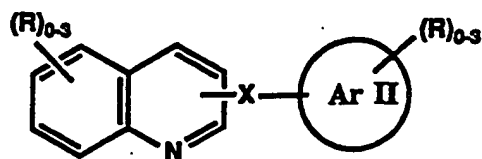
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6. A method according to claim 5 where said compound is described by one of the following formulae:

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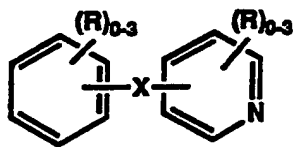


7. A method according to claim 6 where said compound is of the formula



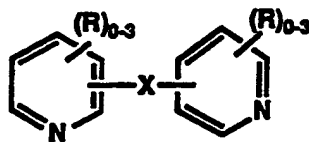
- where $Ar II$ is thienyl, phenyl, pyridyl, quinolinyl, indolyl, furanyl, imidazolyl, 2(1H)-pyridonyl, 1(2H)-isoquinolonyl and thiazolyl and R is hydrogen,
 5 loweralkyl, loweralkoxy, hydroxy or halo.

8. A method according to claim 6 where said compound is of the formula



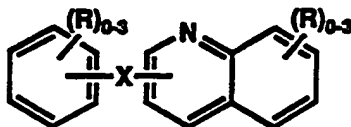
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9. A method according to claim 6 where said compound is of the formula



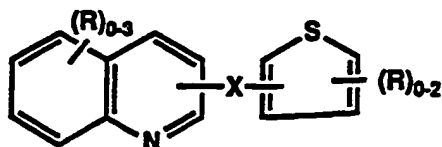
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10. A method according to claim 6 where said compound is of the formula



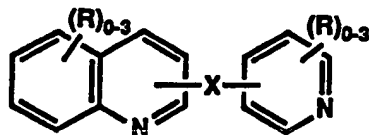
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11. A method according to claim 7 where said compound is of the formula



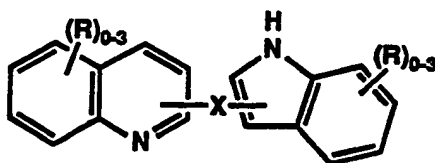
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12. A method according to claim 6 where said compound is of the formula



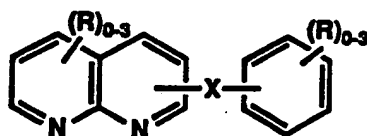
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13. A method according to claim 6 where said compound is of the formula



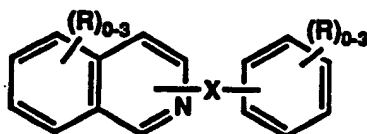
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14. A method according to claim 6 where said compound is of the formula



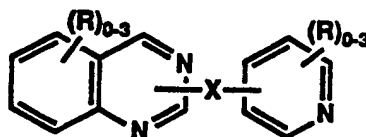
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15. A method according to claim 6 where said compound is of the formula



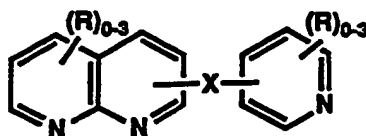
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16. A method according to claim 6 where said compound is of the formula



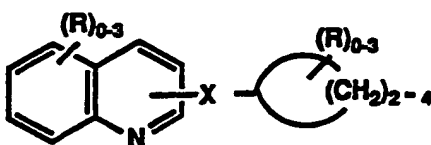
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17. A method according to claim 6 where said compound is of the formula



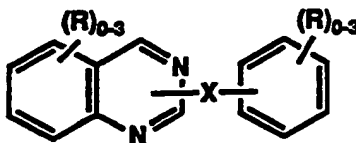
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18. A method according to claim 6 where said compound is of the formula



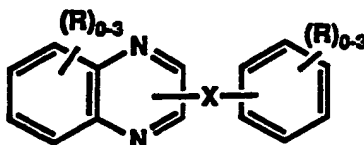
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19. A method according to claim 6 where said compound is of the formula



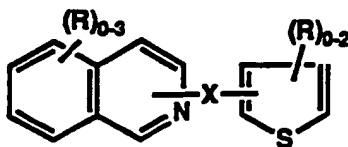
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20. A method according to claim 6 where said compound is of the formula



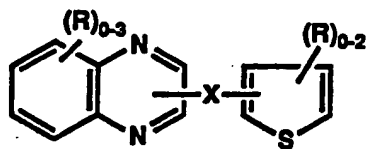
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21. A method according to claim 6 where said compound is of the formula

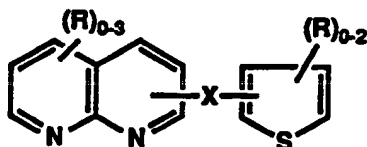


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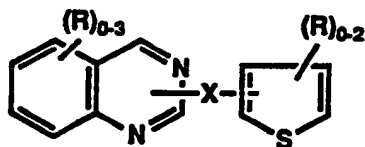
22. A method according to claim 6 where said compound is of the formula



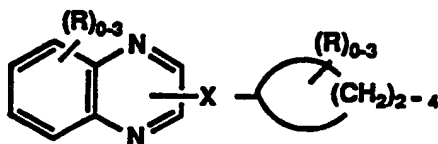
- 5 23. A method according to claim 6 where said compound is of the formula



- 10 24. A method according to claim 6 where said compound is of the formula



- 15 25. A method according to claim 6 where said compound is of the formula



- 20 26. A method according to claim 1 where said compound administered is selected from the group consisting of
 3-(4-methoxyphenyl)-6,7-dimethoxyquinoline;
 3-(thien-3-yl)-6,7-dimethoxyquinoline;
 3-(thien-3-yl)-7-methoxyquinoline;
 25 3-(4-methoxyphenyl)-6,7-dimethoxyquinoline;
 3-(2-chlorothien-2-yl)-6,7-dimethoxyquinoline;
 3-(3-fluoro-4-methoxyphenyl)-6,7-dimethoxyquinoline;
 2-(4-methoxyphenyl)-6,7-dimethoxyquinoxaline;

- 3-(2-chlorothiophen-2-yl)-5,7-dimethoxyquinoline;
2-phenyl-6,7-dimethylquinoxaline;
2-(thien-3-yl)quinoxaline;
6,7-dimethyl-2-(thien-3-yl)-quinoxaline;
5 3-(4-methoxyphenyl)-6,7-dimethoxyquinoline;
3-(thien-3-yl)-6,7-dimethoxyquinoline;
3-(thien-3-yl)-7-methoxyquinoline;
3-(4-methoxyphenyl)-6,7-dimethoxyquinoline;
3-(2-chlorothiophen-2-yl)-6,7-dimethoxyquinoline;
10 3-(3-fluoro-4-methoxyphenyl)-6,7-dimethoxyquinoline;
2-(4-methoxyphenyl)-6,7-dimethoxyquinoxaline;
3-(2-chlorothiophen-2-yl)-5,7-dimethoxyquinoline;
3-(thien-3-yl)-6,7-dimethylquinoline;
3-(1-cyclopent-1-enyl)-6,7-dimethoxyquinoline;
15 3-cyclopentyl-6,7-dimethoxyquinoline;
4-(3-phenylpropyloxy)-6,7-dimethoxyquinoline;
3-(thien-3-yl)-6,7-dimethoxyquinoline-N-oxide;
3-(2-chlorothiophen-5-yl)-5,7-dimethoxyquinoline;
3-(3-fluoro-4-methoxyphenyl)-6,7-dimethoxyquinoline;
20 3-(3-fluorophenyl)-6,7-dimethoxyquinoline;
4-(2-phenylethoxy)-6,7-dimethoxyquinoline;
3-(4-methoxybenzyloxy)-6,7-dimethoxyquinoline;
2-(4-methoxyphenyl)-6,7-dimethoxyquinoxaline;
2-(thien-3-yl)-6,7-dimethoxyquinoxaline;
25 2-phenyl-6,7-dimethoxyquinoxaline;
6,7-dimethyl-2-(thien-3-yl)-quinoxaline;
2-phenyl-6,7-diethoxyquinoxaline;
2-(3-thienyl)-6,7-diethoxyquinoxaline;
2-(5-chloro-2-thienyl)-6,7-diethoxyquinoxaline;
30 2-(5-chloro-2-thienyl)-6,7-dimethoxyquinoxaline;
3-(3-fluoro-4-methoxyphenyl)-7-fluoroquinoline;
3-(thien-3-yl)-5,7-dimethylquinoline;
3-(5-chlorothiophen-2-yl)-6,7-dimethylquinoline;
3-(thien-3-yl)-6,7-difluoroquinoline or
35 3-(4-methoxyphenyl)-7-methoxy-1-naphthalenol.

27. A method for the treatment of psoriasis in a patient suffering from such disorder comprising administering to said patient an effective anti-psoriatic composition according to claim 2.
- 5 28. A method for the treatment of atherosclerosis in a patient suffering from such disorder comprising administering to said patient an effective anti-atherosclerotic composition according to claim 2.
29. A method for the treatment of vascular reocclusion in a patient suffering
10 from such disorder comprising administering to said patient an effective amount of a composition according to claim 2.
30. A method according to claim 29 where said disorder results from an angioplastic procedure.
- 15 31. A compound selected from the group consisting of:
- 3-(4-methoxyphenyl)-6,7-dimethoxyquinoline;
 - 3-(thien-3-yl)-6,7-dimethoxyquinoline;
 - 3-(thien-3-yl)-7-methoxyquinoline;
 - 20 3-(4-methoxyphenyl)-6,7-dimethoxyquinoline;
 - 3-(2-chlorothien-2-yl)-6,7-dimethoxyquinoline;
 - 3-(3-fluoro-4-methoxyphenyl)-6,7-dimethoxyquinoline;
 - 2-(4-methoxyphenyl)-6,7-dimethoxyquinoxaline;
 - 3-(2-chlorothien-2-yl)-5,7-dimethoxyquinoline;
 - 25 3-(thien-3-yl)-6,7-dimethylquinoline;
 - 3-(1-cyclopent-1-enyl)-6,7-dimethoxyquinoline;
 - 3-cyclopentyl-6,7-dimethoxyquinoline;
 - 4-(3-phenylpropyloxy)-6,7-dimethoxyquinoline;
 - 3-(thien-3-yl)-6,7-dimethoxyquinoline-N-oxide;
 - 30 3-(2-chlorothiophen-5-yl)-5,7-dimethoxyquinoline;
 - 3-(3-fluoro-4-methoxyphenyl)-6,7-dimethoxyquinoline;
 - 3-(3-fluorophenyl)-6,7-dimethoxyquinoline;
 - 4-(2-phenylethoxy)-6,7-dimethoxyquinoline;
 - 3-(4-methoxybenzyloxy)-6,7-dimethoxyquinoline;
 - 35 2-(4-methoxyphenyl)-6,7-dimethoxyquinoxaline;
 - 2-(thien-3-yl)-6,7-dimethoxyquinoxaline;
 - 2-phenyl-6,7-dimethoxyquinoxaline;

- 5 6,7-dimethyl-2-(thien-3-yl)-quinoxaline;
2-phenyl-6,7-diethoxyquinoxaline;
2-(3-thienyl)-6,7-diethoxyquinoxaline;
2-(5-chloro-2-thienyl)-6,7-diethoxyquinoxaline;
2-(5-chloro-2-thienyl)-6,7-dimethoxyquinoxaline;
3-(3-fluoro-4-methoxyphenyl)-7-fluoroquinoline;
3-(thien-3-yl)-5,7-dimethylquinoline;
3-(5-chlorothien-2-yl)-6,7-dimethylquinoline;
3-(thien-3-yl)-6,7-difluoroquinoline or
10 3-(4-methoxyphenyl)-7-methoxy-1-naphthalenol.

32. A pharmaceutical composition wherein the active ingredient is selected from the compounds of Claim 31.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US92/03736

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07C 43/21; C07D 215/18; 215/20; 43/21; A61K 31/44 31/50; 31/495

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Chemical Abstracts 1902-1991 Formula index.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A, 4,661,499 (YOUNG ET AL) 28 APRIL 1987 See entire reference.	31 & 32
A	N, CHEMICAL Abstract, volume 103, Abst. No. 1232922, Barker et al., J. Chemical Soc. PERKIN. TRANS. 1985, (2), 275-81 (ENG.) See entire document.	31-32
A	M. CHEMICAL ABSTRACTS., Volume 108, N. Chemical Abstracts, No. 55860; Epling et al, J. HETEROLYCL. chem. 1987, 24(3) 853-7 (ENG.), See entire reference.	



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	* T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* A* document defining the general state of the art which is not considered to be part of particular relevance	* X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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* P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

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Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US92/03736

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

544/354; 353; 546/155; 167;180; 546/633; 514/248;249;300;307;311,314,345,347

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